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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561
Filed 08/21/98

GROUP 1644
Examiner Ewoldt

ANTI-IDIOTYPIC ANTIBODIES
OF VASCULAR ENDOTHELIAL
GROWTH FACTOR AND
USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Pierre Fons, hereby declare as follows:

My relevant background and experience are set forth on the attached c.v. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, hat one of ordinary skill in the art would be able to make and use the claimed invention.

As a student in 1997 in the laboratory of Doctor Jean Plouet, I was given the task to reproduce the double immunization in mice that had been previously performed in rabbits. I produced several hybridomas, and I used the screening methods described in the present patent application filed by Doctor Jean Plouet, including the Radio Receptor Assay. It took only routine experimentation to isolate and identify anti-id immunoglubulins from mice corresponding to the Ig2 J fraction of the present application. It was a matter of routine experimentation over a time period of six months to produce monoclonal antibodies from a range of candidate B-lymphocytes and to identify those having the claimed binding specificity. Six months is a classical amount of time necessary to perform a double immunization in mice.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

PIERRE FONS

Date

February , 2002

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561 GROUP 1644
Filed 08/21/98 Examiner Ewoldt

ANTI-IDIOTYPIC ANTIBODIES
OF VASCULAR ENDOTHELIAL
GROWTH FACTOR AND
USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Pierre-Andre Cazenave, hereby declare as follows:

My relevant background and experience are set forth on the attached c.v. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, that one of ordinary skill in the art would be able to make and use the claimed invention.

Given the showing in the specification that about 15 to 20% of rabbits produce the anti-idiotypic antibodies having the claimed binding specificity, I confirm that a person skilled in the field of anti-idiotypic science would have at least a "reasonable expectation" that a comparable percentage of mice would produce an anti-idiotypic antibody having that binding specificity. In view of the results produced in rabbits, and when following most of the steps described in the present specification, comparable results in mice would have been expected without undue experimentation. Anti-idiotypic reactions occur against a given antigen in all mammalian species. The screening procedure of the present application has been established as an assay measuring the inhibition of recombinant human VEGF toward recombinant human VEGFR2 by immunoglobulin. Therefore, the origin of anti-idiotypic antibodies, whether from rabbits or mice, is not a limiting step.

I also confirm that, given the screening methods described in the present specification, an analysis of the specificity of mice antibodies by Radio Receptor Assay would involve only routine experimentation to identify anti-id immunoglobulin corresponding to the Ig2 J fraction of the present specification. It is only a matter of time and routine experimentation to produce monoclonal antibodies from potential B-lymphocytes and to identify those having the claimed binding specificity.

Having seen the results of the experiments using Fab fragments, my understanding is that they display anti-angiogenic properties functionally similar to the original antibodies conjugated with cytotoxic agents: the Fab are, like the original antibodies, ligands to KDR or flk-1, and not to flt-1 They bind to the KDR receptor and block it, hence preventing VEGF to be internalized into endothelial cells and to induce their proliferation. Accordingly, Fab fragments prevent proliferation of endothelial cells, and act functionally like the antibodies of the specification conjugated with cytotoxic agents.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on

information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

	Date
PIERRE-ANDRE CAZENAVE	March , 2002

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jean PLOUET et al.

Serial No. 09/091,561 GROUP 1644

Filed August 21, 1998 Examiner G. Ewoldt

ANTI-IDIOTYPIC ANTIBODIES OF
VASCULAR ENDOTHELIAL GROWTH FACTOR
AND USE THEREOF AS DRUGS

TRANSLATOR'S CERTIFICATE OF VERIFICATION

Commissioner for Patents

Washington, D.C. 20231

Sir:

I, Andrew Patch of Young & Thompson, 745 South 23rd Street, Arlington, VA 22202

Hereby declare

1. That, I am competent in French to English translations, and

2. That, to the best of my knowledge and belief, hereby state that the term "notamment" may be translated from French to English as "for example" or "notably".

Respectfully submitted,

Andrew J. Patch

March 25, 2002

#28
GND

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561
Filed 08/21/98

GROUP 1644
Examiner Ewoldt

ANTI-IDIOTYPIC ANTIBODIES
OF VASCULAR ENDOTHELIAL
GROWTH FACTOR AND
USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Jean Plouet, hereby declare as follows:

I am the same Jean Plouet named as an inventor in the above-identified patent application. My relevant background and experience are set forth on the attached c.v. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, that one of ordinary skill in the art would be able to make and use the claimed invention.

Further, I declare that the Ig2 J fraction described in the present specification, although presumably including some anti-idiotypic antibody that binds to both flk and flt, nevertheless contains a sufficient proportion of the claimed antibody (binding to flk but not flt) as to display the strong difference in binding profiles shown in present Figs. 1A and 1B. Therefore, even the polyclonal fraction is useful as such (although perhaps not commercially), and this is demonstrated by the experiments in the specification showing that the Ig2 J fraction promotes tumor angiogenesis, and hence is valuable as a selective targeting agent.

As it is confirmed in a separate affidavit signed by Professor Cazenave, from the Pasteur Institute in Paris, given the showing in the specification that about 15 to 20% of rabbits produce the anti-idiotypic antibody having the claimed binding specificity, a person skilled in the field of anti-idiotypic science would have at least a "reasonable expectation" that a comparable percentage of mice would produce an anti-idiotypic antibody having that binding specificity. In view of the results produced in rabbits, comparable results in mice would have been expected without undue experimentation, when following most of the steps described in the specification.

As it is confirmed in the same affidavit signed by Professor Cazenave, I also confirm that given the screening methods described in the present specification, an analysis of the specificity of mice antibodies by Radio Receptor Assay would involve only routine experimentation to isolate and identify anti-id immunoglobulin corresponding to the Ig2 J fraction of the present specification. It is only a matter of time and routine experimentation to produce monoclonal antibodies from the candidate B-lymphocytes and to identify those having the claimed binding specificity. It is also useful to reemphasize that successful production of monoclonal antibodies have in fact been performed subsequent to the filing of the International application, and that no unusual difficulty was encountered. In fact, it took only six months to achieve the results reported in my earlier filed declaration. Six months is a classical amount of time necessary to perform double

immunization in mice. That point is further confirmed in a separate affidavit by Doctor Pierre Fons, who was at the time a student of mine and the principal operator of this double immunization.

It is also useful to reemphasize that successful production of monoclonal antibodies has in fact been performed subsequent to filing of the International application, and that no unusual difficulty was encountered. In fact, it took only 6 months to achieve the results reported in my earlier Rule 132 declaration, which is a classical amount of time necessary to perform the double immunization in mice. That point is also confirmed in a separate affidavit by Doctor Pierre Fons, who was at the time a student of mine and the principal operator of this double immunization.

It is also useful to emphasize that Fab fragments display anti-angiogenic properties functionally similar to the original antibodies conjugated with cytotoxic agents. As it was pointed out by USPTO, it is absolutely exact that "Fab fragment cannot exert the same functional activity as the antibodies, since the Fab cannot induce "dimerization, internalization and cell proliferation." In fact, since the Fab are, like the original antibodies, ligands to KDR or flk-1, and not to flt-1 (claim 9, initial number), they link to this receptor and block it, hence preventing VEGF present in the tumor to be internalized into endothelial cells and to induce their proliferation. Accordingly, Fab fragments prevent proliferation of endothelial cells, and act functionally like the antibodies of the specification conjugated with cytotoxic agents.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

	Date
JEAN PLOUËT	March , 2002

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561 GROUP 1644
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ANTI-IDIOTYPIC ANTIBODIES OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

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I am the same Jean Plouet named as an inventor in the above-identified patent application. My relevant background and experience are set forth on the attached c.v. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, that one of ordinary skill in the art would be able to make and use the claimed invention.

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Six months is a classical amount of time necessary to perform double immunization in mice. That point is further confirmed in a separate affidavit by Doctor Pierre Fons, who was at the time a student of mine and the principal operator of this double immunization.

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J. Plouët

JEAN PLOUËT

3/19/2002

Date

Curriculum vitae of the candidate

Jean PLOUET
Born August 11 1951 à Paramé (35), married, 2 daughters.
Diplômes :

Médecine
MD, Nantes, 1977.
Certified in Immunology, 1977.
Specialisation in Immunology, 1978.

Sciences
Certificate of Structural and Metabolic Biochemistry, Nantes, 1976.
Certificate of Animal Physiology, Nantes, 1977.
Post-degree Course in Eucaryotic Molecular Biology Paris VII, 1978.
PhD,. Fondamental Biochemistry, Paris VII, 1981.

Activités Hospitalo-Universitaires
- Lecturer in Biochemistry PCEM1, Université de Nantes
1976-1978 Lecturer
1978-1979 Assistant Professor
- MD in the Biochemistry Laboratory, Nantes Hospital
1977-1979 Vacations
1979-1980 Assistant Professor

Activités de Recherche.
- U.118 INSERM, Paris
1980-1981 Fellow of the Ligue Nationale contre le Cancer
1981-1984 Assistant Research Professor II, CNRS (COMMISSION 28)
- U.86 INSERM, Paris
1984-1985 Assistant Research Professor II, CNRS
1985-1987 Assistant Research Professor I, CNRS
- U.C.S.F., (Cancer Research Institute), San Francisco
1987-1988 Assistant Research Biochemist
- U.86 INSERM, Paris
1989-1990 Assistant Research Professor I, CNRS
-UPR 9008 CNRS, Toulouse.
1991 ATIPE Laureate, Team leader
1992 Associate Research Professor II CNRS

1999 Team leader « Plasticity of the endothelial cell » à l'UMR CNRS 5089
Director of the GDR 1927 CNRS « Angiogénèse »
CSO of the company AbTECH

1- PUBLICATIONS IN INTERNATIONAL JOURNALS

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3. Barritault D., Plouët J., Courty S., Courtois Y., 1983.
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4. Plouët J., Olivié M., Courtois J., Courtois Y., Barritault D. (1983).
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6. Plouët J., 1988.
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7. Hamel C., Moukadiri H., Favard C., Dorey C., Plouët J., 1990
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8. Moukadiri H., Favard C., Bikfalvi A., Plouët J., 1992.
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9. Plouët J., Moukadiri H., Gouzi L., Malavaud B., Ruchoux M.-M., 1992.
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11. Plouët J., Sordello S., Malavaud B., Ortéga N., 1996.
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12. Plouët J., Malavaud B., Sordello S., Ortéga N., 1996.
Rôles du VEGF dans la progression tumorale.
Eurocancer 96, 197-198 ; M. Boiron, M. Marty eds. John Libbey Eurotext.

13. Sordello S., Faucon B., Plouët J., 1998.
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14. Plouët J., 1999.
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15. Sordello S., Fons P., Malavaud B., Plouët J., 1998.
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16. Hutchings H., Ortéga N., Tournier J-F, Plouët J., 1998.
Endothelial cells.
Encyclopedic reference of vascular biology and pathology, A. Bikfalvi Ed, Springer-Verlag, 80-85.

PATENTS AND LICENCES

1989 Brevet UCSF N° 479.60 "ENDOTHELIAL CELL GROWTH FACTOR: METHODS OF ISOLATION AND EXPRESSION (MURINE)"
Inventeurs : N. Ferrara et D. Gospodarowicz, J. Plouët
Licence concédée à Genentech

1995 Brevet CNRS N° 95.15243; PCT/FR/96/02041
"ANTICORPS ANTI-IDIOTYPIQUES DU FACTEUR DE CROISSANCE ENDOTHELIALE VASCULAIRE ET LEUR UTILISATION COMME MEDICAMENTS"
Inventeurs : J. Plouët , N. Ortéga, F. Jonca, MM Ruchoux.
Licence concédée à AbTECH

1999 Brevet CNRS 9908779
"ANTICORPS ANTI-IDIOTYPIQUES DU FACTEUR DE CROISSANCE DES FIBROBLASTES 1 ET LEUR UTILISATION COMME MEDICAMENTS"
Inventeurs : J. Plouët, S. Sordello, B. Malavaud, J. Jouanneau, P. Savagnier, J-P Thierry.
Licence concédée a AbTECH.

2000 Brevet Institut Pasteur-CNRS-Université Paris XIII, N° 193396
« PEPTIDE MIMANT LE FACTEUR DE CROISSANCE ENDOTHELIALE VASCULAIRE (VEGF-HYBRIDOME)-APPLICATION A LA THERAPIE DES TUMEURS. »
Inventeurs : R. Tournaire, C. Demangel, C. Derbin, G. Perret, J-C Mazié, J. Plouët.
Licence concédée à Bristol Myers

2001 Brevet CNRS-INSERM-AbTECH N° 01-10554
« UTILISATION DE MOLECULES SOLUBLES HLA DE CLASS 1 ET LEUR UTILISATION COMME MEDICAMENTS ANTI-ANGIOGENIQUES. »
Inventeurs : , J. Plouët, P. Fons, F. L'Faqihi, P. Lebouteiller

Licence concédée à AbTECH

2001 Brevet CNRS-AbTECH N° 01-10553
« ANTICORPS ANTI-IDIOTYPIQUES DE MOLECULES HLA DE CLASSE I ET LEUR UTILISATION POUR LA PREPARATION DE COMPOSITIONS DESTINEES A INHIBER L'ACTIVATION VASCULAIRE. »
Inventeurs : J. Plouët, P. Fons, M. Trombe.Licence concédée à AbTECH

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561
Filed 08/21/98

GROUP 1644
Examiner Kwoldt

ANTI-IDIOTYPIC ANTIBODIES OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Pierre-André Cazenave, hereby declare as follows:

My relevant background and experience are set forth on the attached C.V. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, that one of ordinary skill in the art would be able to make and use the claimed invention.

Given the showing in the specification that about 15 to 20% of rabbits produce the anti-idiotypic antibodies having the claimed binding specificity, I confirm that a person skilled in the field of anti-idiotypic science would have at least a "reasonable expectation" that a comparable percentage of mice would produce an anti-idiotypic antibody having that binding specificity. In view of the results produced in rabbits, and when following most of the steps described in the present specification, comparable results in mice would have been expected without undue experimentation. Anti-idiotypic reactions occur against a given antigen in all mammalian species. The screening procedure of the present application has been established as an assay measuring the inhibition of recombinant human VEGF toward recombinant human VEGFR2 by immunoglobulin. Therefore, the origin of anti-idiotypic antibodies, whether from rabbits or mice, is not a limiting step.

I also confirm that, given the screening methods described in the present specification, an analysis of the specificity of mice antibodies by Radio Receptor Assay would involve only routine experimentation to identify anti id immunoglobulin corresponding to the IgG 3 fraction of the present specification. It is only a matter of time and routine experimentation to produce monoclonal antibodies from potential B-lymphocytes and to identify those having the claimed binding specificity.

Having seen the results of the experiments using Fab fragments, my understanding is that they display anti-angiogenic properties functionally similar to the original antibodies conjugated with cytotoxic agents: the Fab are, like the original antibodies, ligands to KDR or flk-1, and not to flt-1 They bind to the KDR receptor and block it, hence preventing VEGF to be internalized into endothelial cells and to induce their proliferation. Accordingly, Fab fragments prevent proliferation of endothelial cells, and act functionally like the antibodies of the specification conjugated with cytotoxic agents.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on

information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Pierre-André Cazenave 3/25/2002

PIERRE-ANDRE CAZENAVE Date

CURRICULUM VITAE

CAZENAVE Pierre-André
Born : February 12, 1940 at SEES (Orne), France
Nationality : French

Title and Position
Assistant Professor (Chef de Laboratoire) at the Institut Pasteur, 1976-1987
Professor at the Institut Pasteur, since 1987
Head of Analytical Immunochemistry Unit at the Institut Pasteur, since 1978
Head of the Department of Immunology, Institut Pasteur, 1994-1997
Director of the URA (Unité de Recherches Associées) D1961 of CNRS, since 1995
Deputy Director of the LBA (Foreign Associated Laboratory) of CNRS at the Instituto Gulbienkian de Ciencia, Portugal

Education
Doctor ès Sciences, Paris, 1974
Research Assistant at the Faculty of Sciences, Paris, 1967-1971
Assistant Professor in Biochemistry at the University Paris 7, 1971-1974
Lecturer in Immunology at the Pierre and Marie Curie University, 1974
Professor of Immunology at the Pierre and Marie Curie University, since 1975

Distinctions
Prize "Céline", 1979
Member of the European Molecular Biology Organization, 1981
Prize "Behring-Metchnikoff", 1988
Member of the European Network of Immunology Institutes, 1990
President of the French Society of Immunology, 1992-1995

Administrative Responsabilities
Member of different CNRS and INSERM National Committees between 1980 and 1994
Member of the National Council of the French Universities (1982-1990)
Director of PhD degree Courses in Immunology at the Pierre and Marie Curie University (Paris 6) since 1978
Director of the International Relations of the Institut Pasteur, since 2000

Editorial Board
Biochimie, 1975-1976
Annales d'Immunologie (Institut Pasteur) 1976-1989
Molecular Immunology, 1975-1977
European Journal of Immunology, 1981-1989
Hybridoma, 1981-1988
Research in Immunology, 1989-1998
Immunogenetics, 1982-1995
EMBO Journal, 1992-1996

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Serial No. 09/091,561 GROUP 1644
Filed 08/21/98 Examiner Ewoldt

ANTI-IDIOTYPIC ANTIBODIES
OF VASCULAR ENDOTHELIAL
GROWTH FACTOR AND
USE THEREOF AS DRUGS

DECLARATION UNDER RULE 132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Pierre Fons, hereby declare as follows:

My relevant background and experience are set forth on the attached c.v. I make this declaration in support of the present application, and to provide evidence in rebuttal of several contentions in the Official Action of September 25, 2001, hat one of ordinary skill in the art would be able to make and use the claimed invention.

As a student in 1997 in the laboratory of Doctor Jean Plouet, I was given the task to reproduce the double immunization in mice that had been previously performed in rabbits. I produced several hybridomas, and I used the screening methods described in the present patent application filed by Doctor Jean Plouet, including the Radio Receptor Assay. It took only routine experimentation to isolate and identify anti-id immunoglubulins from mice corresponding to the Ig2 J fraction of the present application. It was a matter of routine experimentation over a time period of six months to produce monoclonal antibodies from a range of candidate B-lymphocytes and to identify those having the claimed binding specificity. Six months is a classical amount of time necessary to perform a double immunization in mice.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

PIERRE FONS

DATE

25.03.02

Pierre FONS
17, rue Julia
31500 Toulouse
home phone: 05 62 47 25 67
office phone: 05 61 17 58 36

29 years, born in Toulouse
Married, 1 daughter
e-mail: pierre.fons@sanofi-synthelabo.fr

Ph.D.
Cellular biology and biotechnology

Education

2002 Post-doctoral Research associate Sanofi-Synthélabo.

1997 – 2001 Ph.D. student C.N.R.S Plasticity group of endothelial cells
Thesis director: Jean Plouët - IPBS-Toulouse.

1996 D.E.A : Biomedical engineering. U.T.C-Compiègne.

1994 – 1995 Master Sciences and Technology. Biological / medical engineering Toulouse

1993 D.U.T. Physical measurements-Toulouse

Additional education

1999 Diploma to conduct in-vivo experiments on laboratory animals.
Veterinary National School-Toulouse

1996 Quality Assurance -Toulouse

Professional experiences

1995-1996 DEA fellowship. Physico-chemistry group. Director C. REY-INPT-Toulouse
Calcium phosphate formation on collagen in order to mimic bone structure.
Development of physicochemical analysis.

1996-1997 Quality Assurance manager. Biotecnic (Toulouse) : production of orthopaedic prostheses.
- Modification of the quality handbook
- Implementation of ISO 29001 regulations

1997 – 2001 Ph.D. student C.N.R.S Plasticity group of endothelial cells
Thesis director: Jean Plouët - IPBS-Toulouse.
Control of angiogenesis by systemic approach.
- In vivo experimentation
- Cellular cultures, cellular fusion
- Western blot and cross-link
- Flow Cytometry
- Proteins purifications (FPLC,HPLC, RRA)
- Cellular transfection

Publication:

- Fons P., Malavaud B., Venat L., Plouët J., Strategies anti-angiogéniques en cancérologie, Bulletin de l'Académie Nationale de Médecine, 2000, 184, n°3, 579-587.
- Sordello S., Fons P., Malavaud B., Plouët J., VEGF, Encyclopedic reference of vascular biology and pathology, A.Bikfalvi Ed, 2000, Springer-Verlag, 322-331.

Patents:

Patent n° 01/10554: Utilisation of soluble HLA molecules of class I for the preparation of pharmaceutics compositions in order to inhibit angiogenesis.
Patent n° 01/10553: Antibodies anti-idiotypic of HLA molecules of class I and their use for the preparation of compositions to inhibit vascular activation.

Communication:

Building specific vectors for angiogenesis.